SUPPORT FOR THE AMENDMENTS

The specification at page 11 has been amended to insert a description of Figure 35. Support for this amendment is provided by page 27, lines 19-36 of the substitute specification filed on May 20, 2008.

No new matter has been added.

REMARKS

Claims 8, 10, and 11 are pending in the present application.

The rejection of Claims 8, 10, and 11 under 35 U.S.C. §103(a) over Crapo et al in view of Brurok et al and Towart et al is respectfully traversed.

Crapo disclose a method of preventing or treating cancer including administration of mimetics of SOD, in particular porphyrins and tetrapyrroles, preferably manganic derivatives thereof. They also disclose that these compounds can be used with other chemotherapeutic agents, such as bleomysin, cisplatin, adriamycin, and camptothicen and that such associations allow an increase in the anti-tumor effect of chemotherapy and reducing toxicity to normal tissues. Thus, "a wide variety of normal tissues can be protected... including lung tissue, mucosa, gastrointestinal tract tissue, leucocytes, hair follicles, skin and bone marrow" (see page 9, lines 9-12). Conspicuous in its absence, however, is mangafodipir MnDPDP).

Towart disclose that chelating agents, including mangafodipir are effective in reducing the cardiotoxicity of paclitaxel (taxol) and anthracyclines, such as doxorubicin (adriamycin). Towart do not disclose or suggest that mangafodipir may be useful in combination with other antitumor agents than anthracyclines and paclitaxel. In particular, Towart do not suggest at all that they can be used in combination with platinum derivatives, such as cisplatin or oxaliplatin, which have a mechanism of action which is quite different from the ones of anthracyclines and paclitaxel.

Brurok merely relates to a general background of the field and states that mangafodipir possesses SOD mimetic activity.

Notwithstanding the Examiner's allegations to the contrary, the skilled artisan would not have been motivated to replace the mimetics of SOD disclosed by Crapo with the SOD mimetic disclosed by Towart.

In Crapo, only one example of the seven total relates to the study of the effects of the use of a SOD mimetic in a treatment with another chemotherapeutic agent: example 3 illustrates that MnTBAP allows attenuating bleomycin-induced lung fibrosis in mice. This example does not show that MnTBAP allows an increase in the cytotoxic effect of bleomycin on tumor cells, indeed the effect on tumor cells is not studied, nor does this example show a decrease on the cytotoxic effect on normal leucocytes as only lung tissue is observed. Thus, Crapo themselves provide no motivation and/or expectation of success in using a SOD mimetic with another anti-tumor agent other than bleomycin.

The examples of Towart illustrate the cardioprotective properties of mangafodipir on murine cardiac cells in culture, with respect to the cardiotoxicity of two antracyclines: doxorubicin and daunomycin. Nevertheless, Towart does not disclose or suggest any increase in the antitumor effect arising from mangafodipir. On the contrary, Towart indicate that the use of metal chelates can make it possible to increase the effectiveness of the treatment by administering higher amounts of the antitumor agent with which they are associated (page 2, second paragraph). In contrast, in the present application, mangafodipir when associated with an antitumor agent makes it possible to increase the effectiveness of the treatment without increasing the amounts of the other anti-tumor agent.

In the same way, Towart fail to disclose or suggest any protective effect on leucocytes by mangafodipir. On the contrary, in order to *reduce the myelotoxicity associated with paclitaxel*, Towart propose to co-administer a hematopoietic growth factor (G-CSF) (see page 8, fifth paragraph). Thus, Towart direct the skilled artisan away from the association of

compounds according to the present invention. The Examiner is reminded that "a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (see MPEP §2141.02).

Furthermore, in Towart (see page 7, third paragraph), the therapeutic application of the metal chelates is an application as a cardioprotective agent. Towart may state that the application is not limited to the use of the metal chelates in association with drugs having cardiotoxic effects, but clearly the concern in this disclosure are pathological conditions in which the hear is at risk. Obtaining a cardioprotective effect is quite different from obtaining a protective effect on normal leucocytes in an anti-cancer chemotherapy combined with an increased cytotoxic effect on tumor cells. More specifically, in the examples of Towart, the cardioprotective effects are shown on isolated cardiac muscle. Thus, it is clear that no antitumor effect or the effect of protection of leucocytes by the tested compounds is observed in Towart.

Even if it were considered that the artisan would have tried replacing one of the SOD mimetics of Crapo with mangafodipir based on the disclosure of Brurok, the skilled artisan would not have found specific direction and/or motivation to combine mangafodipir specifically with cisplatin or oxaliplatin, much less been provided with a reasonable expectation of success in so doing.

As stated above, Crapo disclose the combination of mimetic of SOD with other chemotherapeutic agents such as bleomycin or cisplatin or adriamycin or camptothicen. Nonetheless, only on specific association is disclosed by Crapo: MnTBAP/bleomycin, for which an attenuation of bleomycin-induced lung fibrosis is shown in mice when

administering MnTBAP (see Example 3). Thus, Crapo fail to provide any reasonable basis for using a SOD mimetic with another anti-tumor agent other than bleomycin and certainly do not provide any suggestion of associating a SOD mimetic specifically with cisplatin or oxaliplatin.

Towart disclose the combination of mangafodipir, known as a mimetic of SOD (Brurok) with taxol, or an anthracycline such as daunomycin or adriamycin (doxorubicin).

Thus, nothing in Crapo or Towart would motivate the artisan to select cisplatin in combination with mangafodipir. Indeed, Crapo choose to focus on bleomycin and do not suggest combining a mimetic of SOD specifically with cisplatin and certainly provide no indication that cisplatin should be the one to choose from the list of chemotherapeutic agents recited. Accordingly, from the disclosures of Crapo and Towart, the skilled artisan would, at best, be motivated to combine mangafodipir with adriamycin, but not combining mangafodipir with cisplatin or oxaliplatin.

Even if the Examiner were to have properly established a *prima facie* case of obviousness, which Applicants strongly dispute, Applicants submit that unexpected results are obtained with the method and the pharmaceutical composition of the claimed invention. Further, Applicants submit that "Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness... Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)"

To this end, nothing in the cited art suggested that mangafodipir with either cisplatin or oxaliplatin would allow for an increase in the cytostatic or cytotoxic effects on tumor cells

and for a decrease of the cytotoxic effect on normal leucocytes of an anticancer medicinal product. As stated at page 4, lines 33-34 of the specification, at the time of the present invention "the only cytoprotective agent used to reduce the leucopenia is amiphostine."

Crapo mentions an increase of the anti-tumor effect of chemotherapy as well as a protection of normal tissues. They state "a wide variety of normal tissues can be protected... including lung tissue, mucosa, gastrointestinal tract tissue, leucocytes, hair follicles, skin and bone marrow" (see page 9, lines 9-12). Although protection of leucocytes is mentioned in this sentence, Crapo fails to provide any indication of which association of compounds could be used in order to obtain specific protection of leucocytes and also fail to provide any examples illustrating any of the effects as achieved by the claimed invention.

Towart fails to disclose any method of providing an increase in the cytostatic or cytotoxic effects on tumor cells of an anticancer medicinal product. As a method of providing a decrease in the cytotoxic effect of an anti-cancer drug on normal leucocytes, Towart, in order to reduce the myelotoxicity associated with paclitaxel, propose to co-administer a hematopoietic growth factor (G-CSF) (see page 8, fifth paragraph).

The Examples of the present application show unexpected properties related to the use of mangafodipir compared with the use of another SOD mimetic, MnTBAP, which was the SOD mimetic used in Crapo. There is nothing in Crapo, Towart, or Brurok that would have disclosed or suggested that mangafodipir would have provided a superior result as compared to the SOD mimetic exemplified in Crapo. Thus, this result which was demonstrated by the present application (see Examples 2, 3, and 7) is utterly unexpected in view of the disclosures of Crapo, Towart, and Brurok and was only first discovered by the present inventors.

In particular, Example 3 of the present application shows that mangafodipir inhibits the cytotoxic effect of oxaliplatin on normal leucocytes (see Figure 24), whereas MnTBAP

increases this effect (see Figure 22) (see page 22, first paragraph). Also, in Example 7, two experiments lead to a significantly more important increase of the anti-tumor effect of oxaliplatin by mangafodipir as compared to MnTBAP (see Figure 34, page 27, lines 10-13, Figure 35, and page 28, last sentence).

In view of the foregoing, Applicants submit that the presently claimed invention is not obvious in view of the combined disclosures of Crapo, Towart, and Brurok. Further, Applicants submit that the evidence of record is sufficient to rebut even a *prima facie* case of obviousness.

Withdrawal of this ground of rejection is requested.

Applicants submit that the present application is in condition for allowance. Early notification to this effect is respectfully requested.

Respectfully submitted,

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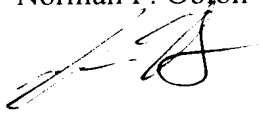

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